DAMAGE CONTROL RESUSCITATION: OPTIMIZING BLOOD COMPONENT USE TO SAVE LIVES OF SEVERELY INJURED SOLDIERS

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ABSTRACT

Medical care in modern warfare is challenged by the use of high-explosive weapons that can induce mass casualties. In the current conflicts, improvements in body armour, the use of tourniquets and hemostatic dressings and in most cases, rapid evacuation times has resulted in higher survival rates than seen in prior wars. A major medical advance in the current conflicts is the initiation of damage control resuscitation for the treatment of severely injured Soldiers, particularly those who require massive transfusion and have dysfunction of their blood clotting system and the highest risk of dying. Recent retrospective analysis of traumatic injuries has revealed that patients who received plasma or a plasma to RBC ratio close to 1:1, had improved survival compared to patients who received standard transfusion therapy of plasma to RBC ratios of 1:4 or greater. As further analysis of the benefits of plasma are realized, research efforts in the laboratory are investigating and characterizing a freeze-dried plasma compared to standard fresh frozen plasma, so the benefits of this blood product can be delivered to far forward locations for the early treatment of severely injured Soldiers.

1. INTRODUCTION

Hemorrhage remains the leading cause of death in conventional warfare, accounting for about 50% of mortality on the battlefield and 30% of those who die from wounds (Bellamy, 1984; Champion et al, 2003). In a recent evaluation of 1000 deaths from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), it was determined that 79% of the potentially survivable deaths were from hemorrhage (Holcomb et al, 2007). Of those, 69% were attributed to non-compressible hemorrhage. Although medics and first responders have effective tourniquets and hemostatic dressings for compressible or external bleeding, they currently have no definitive treatments for such non-compressible injuries. A recent retrospective review of combat deaths in Operation Iraqi Freedom and Operation Enduring Freedom has confirmed that truncal (non-compressible) hemorrhage is the leading cause of potentially survivable deaths (Kelly et al, 2008).

The lethal triad of acidosis, hypothermia and coagulopathy, including that induced by hemodilution from infusion of large volumes of standard resuscitation fluids, was well recognized by the trauma community, but in recent years, it began to be recognized that a about a third of trauma patients have reduced blood clotting capability that may be independent of the above conditions (Brohi et al, 2003; McLeod et al, 2003). Most recently, it was observed that 38% of combat casualties who required a transfusion were coagulopathic on admission (Niles et al, 2008). Thus, the concept of Damage Control Resuscitation (DCR) was developed as a structured intervention aimed to treat the approximately 8-10% of casualties who are the most severely injured, are coagulopathic and are at the greatest risk of dying. These typically are the casualties who require a massive transfusion, defined as receiving > 10 units of blood in a 24 hr period. Together with hypotensive resuscitation practices, DCR focuses on avoiding further dilution of coagulation factors by using appropriate blood products to provide these coagulation factors (plasma), oxygen carrying capability (RBCs) and sufficient volume to restore tissue perfusion and correct metabolism. However, the exact required ratios of blood products for optimal resuscitation remain unknown. Furthermore, frozen plasma is logistically difficult to transport on the battlefield. The studies reported here were conducted retrospectively in trauma patients in theater or performed in experimental swine models to support the DCR program in an effort to optimize the use of blood components in the resuscitation of severely injured Soldiers.

2. MATERIALS AND METHODS

2.1 Human Studies

Retrospective studies from patients with combat-related traumatic injuries were performed from data

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collected at combat support hospitals (CSH) in Iraq. All retrospective studies were approved by the Institutional Review Board of the Brooke Army Medical Center. In one study (Spinella et al, 2008), a retrospective review of medical records at a CSH was performed on 708 patients transfused at least one unit of a blood product, such as RBCs, fresh frozen plasma (FFP) or warm whole blood (WB). Other studies included up to 252 patients who received a massive transfusion defined as greater than 10 units of RBCs in 24 hrs (Borgman et al, 2007; Stinger et al, 2008). Vital signs on admission, injury severity scores, laboratory values, the amount and ratios of blood products used in a 24 hr period, mortality rates and the cause of death were recorded. Vital signs included systolic blood pressure, heart rate and temperature. Laboratory values included pH, base deficit, hematocrit, prothrombin time presented as the International Normalization Ratio (INR) and injury severity score. Laboratory values were obtained by standard clinical techniques. In the massive transfusion patients, patients were divided into tertiles based on the median ratio of plasma to RBCs received. These groups included a low ratio of 1:8 (0:12 to 1:5), a medium ratio of 1:2.5 (1:3 to 1:2.3) and a high ratio of 1:1.4 (1:1.7 to 1:1.2). In other analyses, massive transfusion patients were divided into 2 groups: those that received <0.2 g fibrinogen/unit RBC infused and those that received ≥0.2 g fibrinogen/unit RBC. The fibrinogen to RBC ratio was calculated from the reported standard amounts of fibrinogen contained in each blood component (FFP, platelets, WB, RBCs and cryoprecipitate) as described by Stinger et al (2008).

2.2 Animal Studies

Immature female swine (4/group), weighing about 40 kg, were anesthetized, splenectomized and instrumented with arterial and venous catheters for hemodynamic and blood gas measurements, blood withdrawal and fluid infusion. After baseline recordings each pig was subjected to a femur fracture followed by a 60% hemorrhage and 30-min shock period. They were then made hypothermic (33° C) and hemodiluted with normal saline, and then subjected to a Grade V liver injury. Pigs were resuscitated with plasma or a plasma to RBCs ratio of 1:1 using either standard fresh frozen plasma (FFP) or lyophilized plasma made from type-matched pooled swine FFP (gift from HemCon Medical Technologies Inc, Portland, OR). All animals were monitored for 4 hr after the start of resuscitation or until death.

Hemodynamic and metabolic variables were monitored continuously throughout the experimental period. Blood samples were drawn at baseline, and at times throughout the study for determination of coagulation function, plasma lactate, hemoglobin and hematocrit by standard clinical chemistry techniques. Prothrombin time (PT) and activated thromboplastin time (aPTT) were determined by standard clinical coagulation tests. Thrombelastography (TEG) for overall coagulation function was performed on citrated blood at the pig's body temperature using the TEG 5000 (Haemoscope, Niles, IL). The accuracy of the TEG was verified using quality control standards obtained from Haemoscope. Samples were run in at least duplicate and the following variables were measured: R time, the minutes elapsed until initial fibrin formation is detected; clotting time, the speed of clot formation (time from R until a clot with a fixed firmness is formed); alpha angle, the kinetics of clot formation; and maximum amplitude (MA) which represents the maximum strength or firmness of the developed clot.

For the retrospective human studies, data were analyzed by multivariate logistic regression as described (Spinella et al, 2008; Stinger et al, 2008). In addition, parametric data were analyzed by Student's t-test, while categorical data used the Fisher's exact test. Animal studies were analyzed by Analysis of Variance (ANOVA) with appropriate post-hoc tests adjusted for multiple comparisons. For continuous data, repeated measures ANOVA were employed. In all cases, $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1 Human Studies

Of the 3287 patients admitted to the Combat Support hospital (CSH) with traumatic injuries, 22% received one or more units of a blood product such as RBCs, plasma or fresh whole blood. The median injury severity score (ISS) of the 708 trauma patients requiring a transfusion was 14 (range 9-25), while it was 18 (range 16-25) in the 252 patients requiring massive transfusion.. In addition, in the patients requiring a blood product, 64% were considered in shock based on a base deficit ≥ 4 or a pH ≤ 7.2. Also, 38% were considered to have a bleeding abnormality as defined by an INR ≥ 1.5. Of these 708 patients, 80% received blood but did not require a massive transfusion and 87 died. Patients that died had significantly higher base deficit, INR, ISS score and

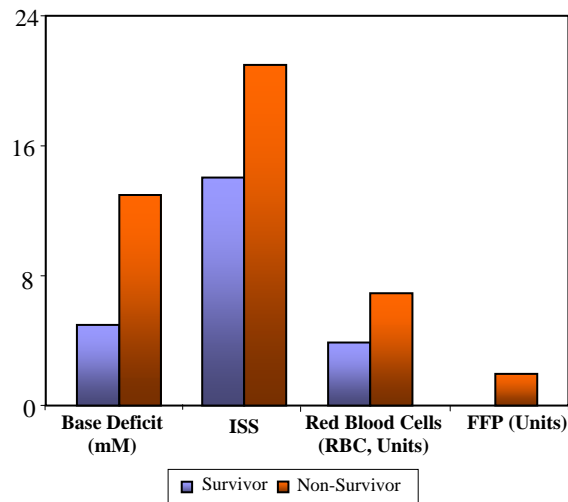received more blood products in comparison to the patients who survived (Fig 1).

Fig 1. Variables in relation to survival in trauma patients who required a blood product. ISS, injury severity score. Data summarized from Spinella et al, J Trauma 64:S69, 2008.

In addition, patients who died had significantly lower heart rate, systolic blood pressure and body temperature on admission compared to the patients who survived. Retrospective analysis of the use of blood products at the CSH showed that survival rates were associated with the injury score, systolic blood pressure, temperature, hematocrit, base deficit, prothrombin time, the amount of RBCs given and the need for massive transfusion. Each unit of transfused FFP was associated with increased survival (OR: 1.17, 95% CI of 1.06-1.29, p = 0.002), whereas each unit of transfused RBCs was independently associated with reduced survival (OR: 0.86, 95% CI of 0.8-0.92, p = 0.001).

Other studies retrospectively reviewed data from 252 casualties requiring massive transfusion; the standard practice of giving a median ratio of 1 unit of plasma for every 8 units of RBCs was associated with a 65% mortality rate (Fig 2).
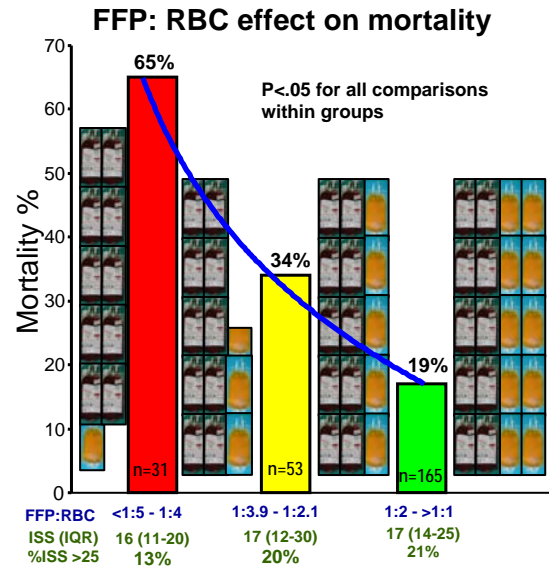

Fig 2. Relationship between survival and ratio of plasma to red blood cells in trauma patients requiring massive transfusion. The blood bags are used to illustrate plasma to RBC ratios of 3.5:20; 2:1 and 1:1 respectively and don't reflect the actual amount of blood or plasma transfused. Modified from Borgman et al, J Trauma 63:805, 2007.

In Soldiers with a similar injury level, mortality was significantly reduced the more plasma they received. When the median ratio of plasma to RBCs was 1:2.5 or 1:1.4, mortality was markedly reduced to 34% and 19% respectively (Fig 2). For these 3 groups, mortality from hemorrhage was 98%, 78% and 37%, respectively. Multivariate analysis revealed that the plasma to RBC ratio was independently associated with overall survival (OR: 8.6; 95% CI 21-85.2, p< 0.003).

Further analysis revealed that similar results were achieved with fibrinogen:RBC ratios $\geq$ 0.2 g fibrinogen/RBC unit. That is, both total mortality and death from hemorrhage were significantly lower in trauma patients who received > 0.2 g fibrinogen/RBC unit (Fig 3).

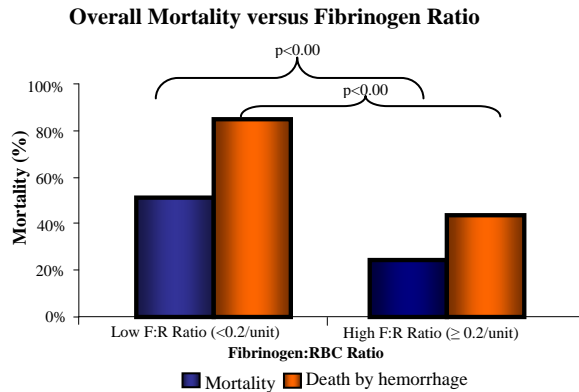**Overall Mortality versus Fibrinogen Ratio**

Fig 3. Relationship between the fibrinogen to red blood cell ratio and all cause mortality and mortality from hemorrhage in trauma patients requiring massive transfusion. Data adapted from Stinger et al. J Trauma 64:S79, 2008.

It appeared that the source of fibrinogen in the high fibrinogen:RBC ratio group was primarily from plasma, whole blood and cryoprecipitate and both groups received equal amounts of RBCs (Fig 4).
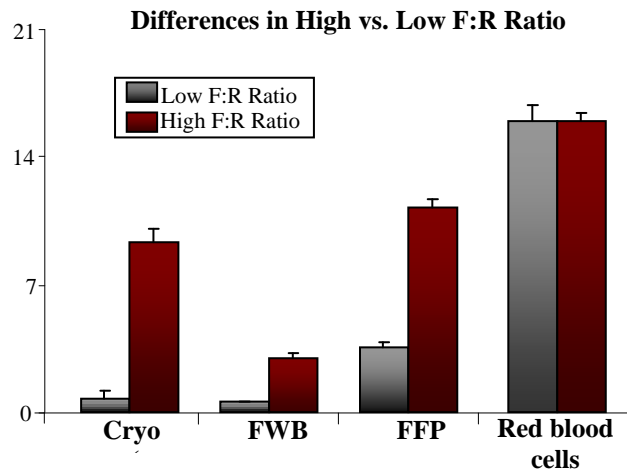
Differences in High vs. Low F:R Ratio

Fig 4: Sources of plasma in trauma patients requiring massive transfusion based on their fibrinogen to RBC ratio. Cryo: cryoprecipitate; FWB: fresh whole blood; FFP: fresh frozen plasma. All data expressed as units. Data adapted from Stinger et al. J Trauma 64:S79, 2008.

In these patients, although both the high and low fibrinogen groups had similarly elevated base deficit, INR and body temperature indicative of hypothermia, overall mortality and death due to hemorrhage in the high fibrinogen: RBC ratio group were significantly

lower (24% vs 52% and 44% vs 85%, respectively) compared to the low fibrinogen:RBC ratio group.

3.2 Animal Studies

As expected the severe hemorrhage in this model significantly reduced the mean arterial pressure and resulted in an elevation in heart rate. The groups that received lyophilized or fresh frozen plasma had similar responses in blood pressure, heart rate and body temperature in response to the multiple trauma/hemorrhage (Fig 5).
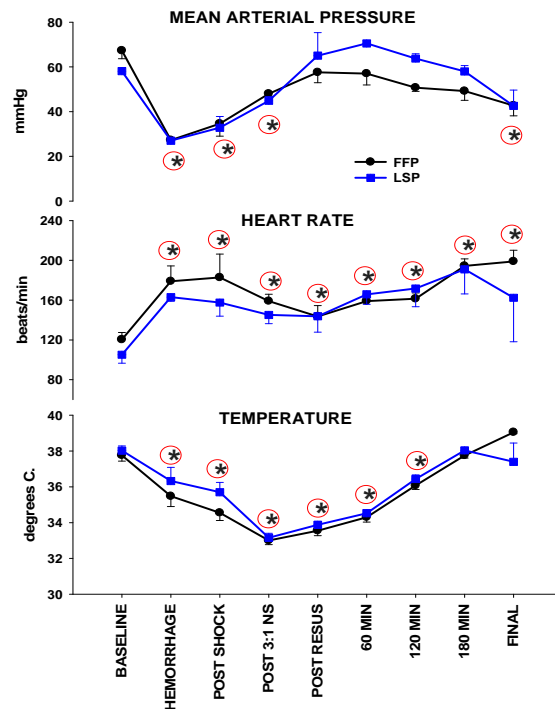

Fig 5: Hemodynamic and temperature responses in cold, coagulopathic swine subjected to hemorrhage and tissue injury and treated with fresh frozen or lyophilized plasma (n=4/gp). *p < 0.05 different from baseline, circled = both groups.

Lyophilized plasma was also as effective as FFP in restoring the measured indices of coagulation, such as standard PT, aPTT and activated clotting time. In addition, no differences were observed between groups treated with FFP vs lyophilized plasma in any of the coagulation or TEG variables including the measures of time to clot initiation (R-time), clot formation rate (alpha angle) and maximum clot strength (MA) (Fig 6).

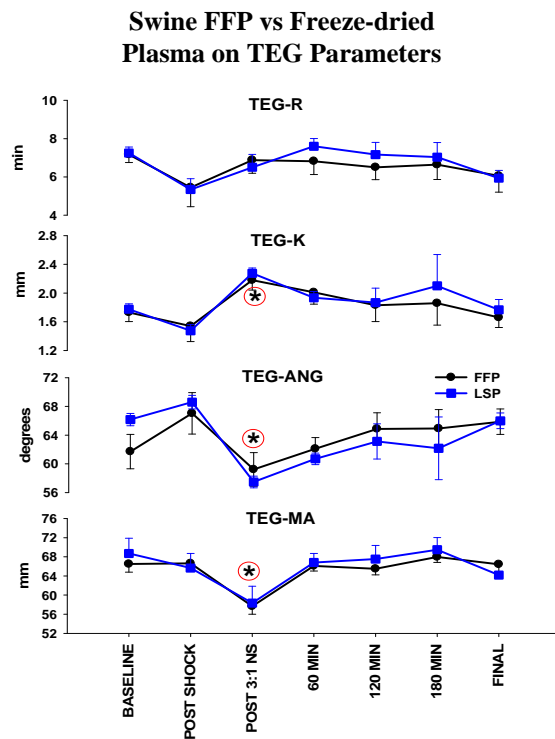**Swine FFP vs Freeze-dried Plasma on TEG Parameters**

Fig 6. TEG variables in cold, coagulopathic swine subjected to hemorrhage and tissue injury and treated with fresh frozen or lyophilized plasma (n=4/gp). p < 0.05 different from baseline, circled = both groups.

4. DISCUSSION

The results of the studies presented here clearly indicate that advances in medical care in the current conflict, including instituting the concept of damage control resuscitation, has served to maintain the lowest case fatality rate (KIA/KIA + DOW) compared to World Wars I and II, Korean Conflict and Vietnam, despite the increase in severity of injuries seen in the last few years of OIF. One of the major advances put forward by damage control resuscitation is the restriction of crystalloid resuscitation fluids and greater use of plasma in patients who require a massive transfusion. Clinical practice guidelines have been placed in Theater and recommend this regimen for patients with massive soft tissue injury, multiple tourniquets or traumatic amputations, laboratory signs of coagulopathy and any condition recognized by the physician that this therapy would be of benefit. The goal of damage control resuscitation is to aim for a 1:1 ratio of plasma to red blood cells. A recent report of a retrospective analysis in the German trauma registry found that in 484 patients who required massive transfusion, early, aggressive treatment with this 1:1 ratio was associated with lower mortality compared to patients who received more red blood cells (Maegele, et al, 2008). For example, patients who received more RBCs than plasma had a 24 hr mortality rate of 33% compared to 17% in patients who received a ratio close to 1:1. This mortality rate was even lower (11%) in massive transfusion patients who received plasma:RBC ratios in excess of 1:1. Based on the military data, a similar retrospective analysis of blood use in massive transfusion patients in 16 US level I civilian trauma centers was undertaken. Of the 466 massive transfusion patients analyzed, 30 d survival improved in the group that received a high plasma:RBC ratio from 40% to near 60% compared to the patients who received the usual higher ratio of RBCs to plasma.

Other aspects of damage control resuscitation not discussed in this current paper involve the use of fresh whole blood and apheresis platelets in theater. Data suggest that the availability of platelets will reduce the need for fresh whole blood, but the availability of platelets is limited. Further work is necessary to verify these claims. In addition, activated recombinant factor VIIa (rFVIIa) has also been used as an intravenous hemostatic product in theater. Although preliminary data suggest that rFVIIa may reduce use of RBCs, and is safe, its use has stirred much controversy and requires further study.

5. SUMMARY AND CONCLUSION

For trauma patients transfused at least one unit of a blood product, FFP amounts were independently associated with improved survival rates, whereas the opposite was observed with RBC infusion. When these data were focused on patients requiring massive transfusion, a plasma:RBC ratio near 1:1 was associated with greater survival to hospital discharge, primarily due to reduced death rates from hemorrhage and possibly related to the fibrinogen content of plasma. This is a significant improvement clinically for a patient population that in general has at least a 25% mortality rate. Thus, based on these retrospective analyses, the recommendation for resuscitation of trauma patients requiring massive transfusion is to give a 1:1 ratio of plasma to RBCs.

As the damage control resuscitation program progresses, the optimal ratios of plasma to RBCs must be further evaluated to reduce mortality in the severely injured patients who require a massive transfusion and have a high risk of dying. This treatment must be coordinated with blood banks to

make most efficient use of these valuable resources. In addition future efforts are needed to focus on bringing the advantages of blood products to far forward locations. One effort would be to have lyophilized human plasma that can be stored at ambient temperature and be reconstituted within minutes. Our studies with lyophilized swine plasma indicate that it is stable at room temperature and can be reconstituted in 10 min. In addition, the animal studies show that the lyophilized plasma retains the beneficial effects of FFP in restoring coagulation function. Taken together, these studies indicate that a change in clinical practice guidelines towards the optimal use of blood products will save lives of severely injured Soldiers.

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